6. Nagler, K., Mauch, D.H., and Pfrieger, F.W. (2001). Glia-derived signals induce synapse formation in neurones of the rat central nervous system. J. Physiol. *533*, 665–679.
7. Ullian, E.M., Sapperstein, S.K., Christopherson, K.S., and Barres, B.A. (2001). Control of synapse number by glia. Science *291*, 657–661.
8. Christopherson, K.S., Ullian, E.M., Stokes, C.C.A., Mullowney, C.E., and Hell, J.W. A., A., Lawler, J., Mosher, D.F., Bornstein, P., and Barres, B.A. (2005). Thrombospondins are astrocyte-secreted proteins that promote CNS synaptogenesis. Cell, in press.
9. Lawler, J. (2000). The functions of thrombospondin-1 and-2. Curr. Opin. Cell Biol. *12*, 634–640.
10. Adams, J.C. (2001). Thrombospondins: multifunctional regulators of cell interactions. Annu. Rev. Cell Dev. Biol. *17*, 25–51.
11. Baenziger, N.L., Brodie, G.N., and Majerus, P.W. (1971). A thrombin-sensitive protein of human platelet membranes. Proc. Natl. Acad. Sci. USA *68*, 240–243.
12. Baenziger, N.L., Brodie, G.N., and Majerus, P.W. (1972). Isolation and properties of a thrombin-sensitive protein of human platelets. J. Biol. Chem. *247*, 2723–2731.
13. Lawler, J.W., Slayter, H.S., and Coligan, J.E. (1978). Isolation and characterization of a high molecular weight glycoprotein from human blood platelets. J. Biol. Chem. *253*, 8609–8616.
14. Asch, A.S., Leung, L.L., Shapiro, J., and Nachman, R.L. (1986). Human brain glial cells synthesize thrombospondin. Proc. Natl. Acad. Sci. USA *83*, 2904–2908.
15. Arber, S., and Caroni, P. (1995). Thrombospondin-4, an extracellular matrix protein expressed in the developing and adult nervous system promotes neurite outgrowth. J. Cell Biol. *131*, 1083–1094.
16. Isaac, J.T. (2003). Postsynaptic silent synapses: evidence and mechanisms. Neuropharmacology *45*, 450–460.
17. Patton, B.L., Cunningham, J.M., Thyboll, J., Kortesmaa, J., Westerblad, H., Edstrom, L., Tryggvason, K., and Sanes, J.R. (2001). Properly formed but improperly localized synaptic specializations in the absence of laminin alpha4. Nat. Neurosci. *4*, 597–604.
18. McMahan, U.J. (1990). The agrin hypothesis. Cold Spring Harb. Symp. Quant. Biol. *55*, 407–418.
19. Sanes, J.R., and Lichtman, J.W. (2001). Induction, assembly, maturation and maintenance of a postsynaptic apparatus. Nat. Rev. Neurosci. *2*, 791–805.
20. O'Brien, R.J., Xu, D., Petralia, R.S., Steward, O., Huganir, R.L., and Worley, P. (1999). Synaptic clustering of AMPA receptors by the extracellular immediate-early gene product Narp. Neuron *23*, 309–323.

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DOI: 10.1016/j.cub.2005.02.013

Maize Genetics: The Treasure of the Sierra Madre

Massive morphological changes occurred during the domestication of maize from wild teosinte. Some of the most important shifts are due to altered expression patterns of major regulatory genes.

Nolan C. Kane and Loren H. Rieseberg

The domestication of maize from the wild grass teosinte was accompanied by major morphological changes, both in vegetative and reproductive structures. How this was accomplished by early farmers, and where this variation in morphology came from, are among the most fascinating puzzles in evolutionary developmental biology. A new study [1] has provided more clues by uncovering the role of one of the major genes apparently involved in maize domestication. Using a candidate gene approach, Gallavotti *et al*. [1] isolated and genetically characterized the *barren stalk1* (*ba1*) gene, which has been proposed as one of only five or six major genes responsible for most of the morphological differences between maize and teosinte, the wild ancestor of maize [2]. This is the second putative domestication gene shown to be involved in dramatic changes in architectural traits, after *teosinte branched1*(*tb1*) [2]. Both genes control the formation of branching and flowering structures, which grow from clusters of stem cells called lateral meristems.

Homozygous *ba1* mutant maize plants are unable to make any lateral branches, which are necessary to produce vegetative branches, female inflorescences or normal male tassels [1]. In contrast, lateral branches grow prolifically on *tb1* mutants, which even produce teosinte-like tassels on the tips [2]. The analyses of Gallavotti *et al*. [1] reveal that *ba1* encodes a transcription factor, and that one of its downstream targets is *tb1*. Interestingly, differences in function of *tb1* alleles from wild teosinte and domesticated corn appear to be solely due to differences in expression patterns [3]; there are no fixed differences in amino acid sequence of the protein.

Thus maize domestication appears to have depended in a large part on changes in the expression patterns of *tb1*, resulting from both changes in the regulatory regions of *tb1* itself, and from changes in one of the proteins that regulates *tb1* expression, Ba1. This cascading effect of alterations in the transcription factor Ba1 changes the expression of *tb1* (and probably other genes as well), which in turn has effects on transcription of many downstream products, leading to massive alterations in branching and inflorescences.

To appreciate the dramatic effect of these and other major domestication genes, it is necessary to understand the incredible differences in morphology between maize and its wild relatives. One of our most important crops, maize was domesticated about 6,000–12,000 years ago [4] from the wild teosinte variety *Zea mays* ssp. *parviglumis*, which still grows wild in the Mexican Sierra Madre. The morphological differences between domesticated maize and wild teosinte are so dramatic that early taxonomists did not recognize their close relationship. While maize has potentially hundreds of unprotected kernels in 4–20 or more rows arranged on a cob, teosinte has 6–12 kernels in two rows and the kernels are protected by a hard, stony covering called a glume [5]. Moreover, when teosinte kernels are ripe, they fall off the plant, while ripe maize kernels remain on the cob [5]. Along with the development of the cob, massive changes in plant architecture are

important, including a reduction in vegetative branching and male tassel formation in maize.

A long-standing debate, mirroring a more general dispute about the genetics of adaptation, concerns the origin of the alleles responsible for the dramatic shift in maize morphology. How did maize evolve from teosinte, which looks so different from modern, domesticated maize? A once widely accepted theory was that hybridization and massive introgression from a closely related species of *Tripsacum* was involved [6]. However, George Beadle put forward an alternative Teosinte Theory [7], which proposed that teosinte was the sole ancestor and that just a few mutations of major effect differentiated teosinte from maize. As Beadle predicted, *Z. mays* ssp. *parviglumis* does appear to be maize's sole ancestor, with no measurable introgression from other species. Surprisingly, much of the variation necessary for the early steps of domestication was likely present in natural variation within teosinte [8]. Thus, early farmers probably selected for new combinations of existing genes, as well as new mutants.

Beadle [7] was also at least partially correct in predicting a few genes with major effects, even though many genes of small effect are also certainly involved. Many experiments focusing on morphological genetics have indicated that five genomic regions were responsible for most of the major morphological differences between maize and teosinte (for example, see [6,9]). Subsequent genomic scans, however, have found many more regions that appear to have experienced strong selection during domestication [10–12]. The role of these additional regions remains to be determined. They may be genes with smaller, but still important, effects on the traits that have already been studied. Alternatively, some of these genes might affect traits whose importance in domestication and improvement has not yet been appreciated.

The genes whose role has been most thoroughly worked out are all, like *ba1* and *tb1*, involved in very obvious, dramatic morphological changes. For instance, *teosinte glume architecture1* (*tga1*) [5] also appears to encode a regulatory protein, governing many aspects of development [13]. A fourth gene of apparently major effect is *zea floricaula/leafy2* (*zfl2*) [14], which is homologous to the *Arabidopsis* gene *LEAFY*, a well-known regulatory gene controlling floral meristem development.

Other, less well-characterized genes thought to be involved in maize domestication include *tassel seed2*(*ts2*) and *dwarf8*(*d8*) [12], both of which are regulatory genes affecting sex determination in meristematic tissue. Notably, *ts2* and *d8* were found through multilocus scans for genetic changes driven by artificial selection, rather than a classic forward genetics (from phenotype to gene) approach.

Although the role of many of these genes is only beginning to be understood, the fact that both forward- and reverse-genetic approaches found developmental regulatory genes is certainly interesting. In fact, virtually all of the maize domestication genes so far examined are regulatory, and many of the differences between wild and domesticated alleles represent changes in expression patterns rather than protein sequence.

Despite mutational and expression data tying *ba1* to inflorescence development and branching in maize, its role in domestication remains uncertain. *Ba1* does map to one of five chromosomal regions (chromosome 3L) that account for most of the morphological differences between maize and teosinte and interacts with *tb1*, as predicted by genetic studies [1]. Contrary to expectations, however, evolutionary analyses have failed to detect evidence of selection during domestication, although selection was detected during maize improvement. To account for this result, Gallavotti *et al*. [1] suggest that the signature of selection during domestication was erased by introgression with a second subspecies of maize, a scenario that is supported by the distribution of *ba1* alleles in maize and teosinte. Nonetheless, further work is needed to link *ba1* to the locus on chromosome 3L known to underlie maize domestication.

What does this information about the genetics underlying maize domestication tell us about adaptation in general? While maize domestication has been heavily influenced by a few very major genes, in some other crops, genes with smaller effects appear to predominate (for example, see [15,16]). It remains to be seen which is the more prevalent pattern in nature. A more universal generalization concerns the importance of changes in regulatory genes and expression patterns during divergence. Evidence for this has been found in a wide array of organisms [17,18] including, perhaps most famously, humans [19]. Another interesting pattern found in maize is that some domesticated alleles appear to have originated not from novel mutations but from segregating variation within ancestral populations [1,8]. Thus, the genetics of maize domestication not only provides details in the story of one of our most important crops, but also has the potential to inform our views of adaptation in response to very strong selection.

References

1. Gallavotti, A., Zhao, Q., Kyozuka, J., Meeley, R.B., Ritter, M., Doebley, J.F., Pe, M.E., and Schmidt, R.J. (2004). The role of barren stalk1 in the architecture of maize. Nature *432*, 630–635.
2. Doebley, J., Stec, A., and Gustus, C. (1995). Teosinte Branched1 and the origin of maize - evidence for epistasis and the evolution of dominance. Genetics *141*, 333–346.
3. Hubbard, L., McSteen, P., Doebley, J., and Hake, S. (2002). Expression patterns and mutant phenotype of teosinte branched1 correlate with growth suppression in maize and teosinte. Genetics *162*, 1927–1935.
4. Matsuoka, Y., Vigouroux, Y., Goodman, M.M., Sanchez, G.J., Buckler, E., and Doebley, J. (2002). A single domestication for maize shown by multilocus microsatellite genotyping. Proc. Natl. Acad. Sci. USA *99*, 6080–6084.
5. Doebley, J. (2004). The genetics of maize evolution. Annu. Rev. Genet. *38*, 37–59.
6. Mangelsdorf, P.C.a.R., R.G. (1938). The origin of maize. Proc. Natl. Acad. Sci. USA *24*, 303–312.
7. Beadle, G.W. (1939). Teosinte and the origin of maize. J. Hered. *30*, 245–247.
8. Clark, R.M., Linton, E., Messing, J., and

Doebley, J.F. (2004). Pattern of diversity in the genomic region near the maize domestication gene tb1. Proc. Natl. Acad. Sci. USA *101*, 700–707.
9. Doebley, J., and Stec, A. (1993). Inheritance of the morphological differences between maize and teosinte - comparison of results for 2 F2 populations. Genetics *134*, 559–570.
10. Vigouroux, Y., McMullen, M., Hittinger, C.T., Houchins, K., Schulz, L., Kresovich, S., Matsuoka, Y., and Doebley, J. (2002). Identifying genes of agronomic importance in maize by screening microsatellites for evidence of selection during domestication. Proc. Natl. Acad. Sci. USA *99*, 9650–9655.
11. Whitt, S.R., Wilson, L.M., Tenaillon, M.I., Gaut, B.S., and Buckler, E.S. (2002). Genetic diversity and selection in the maize starch pathway. Proc. Natl. Acad. Sci. USA *99*, 12959–12962.
12. Tenaillon, M.I., Sawkins, M.C., Long, A.D., Gaut, R.L., Doebley, J.F., and Gaut, B.S. (2001). Patterns of DNA sequence polymorphism along chromosome 1 of maize (Zea mays ssp mays L.). Proc. Natl. Acad. Sci. USA *98*, 9161–9166.
13. Dorweiler, J.E., and Doebley, J. (1997). Developmental analysis of teosinte glume architecture1: A key locus in the evolution of maize (Poaceae). Am. J. Bot. *84*, 1313–1322.
14. Bomblies, K., Wang, R.L., Ambrose, B.A., Schmidt, R.J., Meeley, R.B., and Doebley, J. (2003). Duplicate FLORICAULA/LEAFY homologs zfl1 and zfl2 control inflorescence architecture and flower patterning in maize. Development *130*, 2385–2395.
15. Burke, J.M., Tang, S., Knapp, S.J., and Rieseberg, L.H. (2002). Genetic analysis of sunflower domestication. Genetics *161*, 1257–1267.
16. Grandillo, S., and Tanksley, S.D. (1996). QTL analysis of horticultural traits differentiating the cultivated tomato from the closely related species Lycopersicon pimpinellifolium. Theor. Appl. Genet. *92*, 935–951.
17. Wray, G.A. (2003). Transcriptional regulation and the evolution of development. Int. J. Dev. Biol. *47*, 675–684.
18. Kellogg, E.A. (2004). Evolution of developmental traits. Curr. Opin. Plant Biol. *7*, 92–98.
19. Enard, W., Khaitovich, P., Klose, J., Zollner, S., Heissig, F., Giavalisco, P., Nieselt-Struwe, K., Muchmore, E., Varki, A., Ravid, R., et al. (2002). Intra- and interspecific variation in primate gene expression patterns. Science *296*, 340–343.

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DOI: 10.1016/j.cub.2005.02.014

TOR Signaling: An Odyssey from Cellular Stress to the Cell Growth Machinery

The target of rapamycin (TOR) protein kinase is centrally involved in the coordination of cell growth and proliferation with the availability of growth factors and nutrients. Two recent reports have illuminated a mechanism whereby hypoxic stress dampens TOR signaling in metazoan cells.

Robert T. Abraham

According to Greek mythology, Scylla and Charybdis were two fearsome monsters who threatened Odysseus's fleet of ships as they passed through the Strait of Messina. The names of these legendary creatures have now re-emerged as the identifiers of two cell growth regulatory genes in the fruit fly, *Drosophila melanogaster*. Two recent reports in *Genes and Development* identify *scylla* and *charybdis* and their mammalian orthologs, *REDD1* and *REDD2*, as key players in the stress-response network that coordinates cell growth with the availability of sufficient oxygen to support anabolic metabolism [1,2].

Tuberous Sclerosis Complex Acts Upstream of TOR Signaling

In metazoans, cell and tissue growth is controlled by hormonal factors and by the availability of oxygen and nutrients. Studies in flies and mammals have highlighted the insulin/insulin-like growth factor receptors (InRs) as central components of the hormonal network that controls cell growth [3,4]. These receptors transmit stimulatory signals for protein synthesis and cell mass accumulation, primarily through the sequential activation of phosphoinositide (PI) 3-kinase and the protein kinase AKT (also termed PKB). Until recently, the mechanisms whereby nutrient and oxygen supplies regulated cell growth remained largely mysterious. Compelling evidence now suggests that these bioenergetic precursors stimulate anabolic metabolism, in part, through the activation of TOR, an evolutionarily conserved protein serine/threonine kinase [4]. It now appears that these metabolic signals are relayed to TOR through the heterodimeric tuberous sclerosis complex (TSC) [5]. Tuberous sclerosis is a human autosomal dominant disorder caused by loss of TSC function, and is characterized by the formation of benign tumors, called hamartomas, in organs such as the heart and brain. Interestingly, hamartomatous lesions are also common in several other hereditary diseases in humans, including Cowden's disease and Peutz–Jeghers Syndrome which are caused by functional inactivation of the lipid phosphatase PTEN and of the serine/threonine kinase LKB1, respectively. The phenotypic overlap among these three genetic diseases is more than coincidental, because PTEN, LKB1 and TSC all serve as upstream regulators of TOR signaling [5–7].

The mechanism through which TSC integrates into the TOR signaling pathway and downregulates cell growth has recently been elucidated. TSC is a heterodimeric complex comprising TSC1 and TSC2, and the TSC2 subunit is a GTPase-activating protein (GAP) for the Ras-related GTPase Rheb [5,8]. This small GTPase functions as a positive growth effector downstream of TSC, which antagonizes Rheb function by triggering the conversion of the active GTP-bound form of this protein to the inactive GDP-bound state. When bound to GTP, active Rheb collaborates with TOR to mediate hallmark events associated with TOR signaling, including the phosphorylation of the ribosomal protein S6 kinase (S6K) and